Organic Syntheses

Discussion Addendum for:

Convenient Preparation of 3-Ethoxycarbonyl Benzofurans from Salicylaldehydes and Ethyl Diazoacetate

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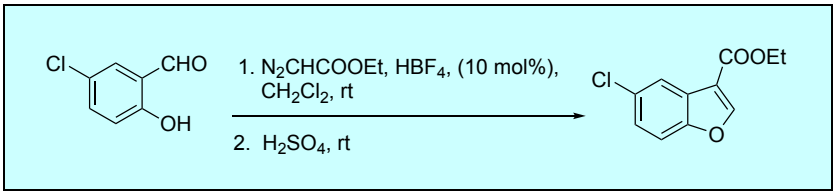

The benzofuran scaffold is an important heterocyclic core component found in several natural products and in polymers.[2,3] Typically, 2,3-disubstituted benzofurans are notable building blocks in many medicinal and biologically active compounds.[4-9] In addition, 3-substituted benzofurans act as anticancer agents,[10] antitubercular agents,[11] antimicrobial agents,[12] antiviral agents,[13] and anti-inflammatory agents.[14] They also act as enzyme inhibitors,[15,16] ischemic cell death inhibitors,[17] receptor agonist-antagonists,[18] and use as diagnostic imaging agents targeting amyloid plaques in Alzheimer's disease.[19] Although syntheses of 2-substituted or 2,3-disubstituted benzofurans are most common, the syntheses of 3-substituted benzofurans are rare.[20-24] In 2004, our group reported an unprecedented reaction of acrylate formation from readily available aldehydes starting materials and ethyl diazoacetate (EDA) in the presence of Brønsted acid, $HBF_4 \cdot OEt_2$.[25] While studying the substrate scope of benzaldehydes to prepare substituted 3-hydroxyacrylates, our group reacted salicylaldehyde with EDA and isolated a very low mass of acrylates with a larger portion of

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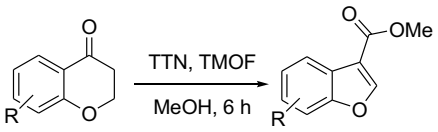
the hemiacetal, 3-ethoxycarbonyl-2-hydroxy-2,3-dihydrofuran. The hemiacetal underwent dehydration in the presence of concentrated H_2SO_4 to form the 3-ethoxycarbonyl benzofuran. The general scope of the reaction was also investigated using various commercially available substituted salicylaldehydes and EDA. The acid catalyzed dehydration via cyclization produced the products in excellent yields.[26]

Alternate methods to prepare 3-alkoxycarbonyl benzofurans

Most alternate syntheses of 3-alkoxycarbonyl benzofuran involve transition metal catalysis. In 1982, Ortar et al. reported the synthesis of 3-methoxycarbonyl benzofurans by the oxidation reaction of chromanones with excess thallium trinitrate (TTN) in methanol in the presence of trimethyl orthoformate (TMOF). The product was isolated as a pale-yellow liquid in only 23% yield (Scheme 1).[27]



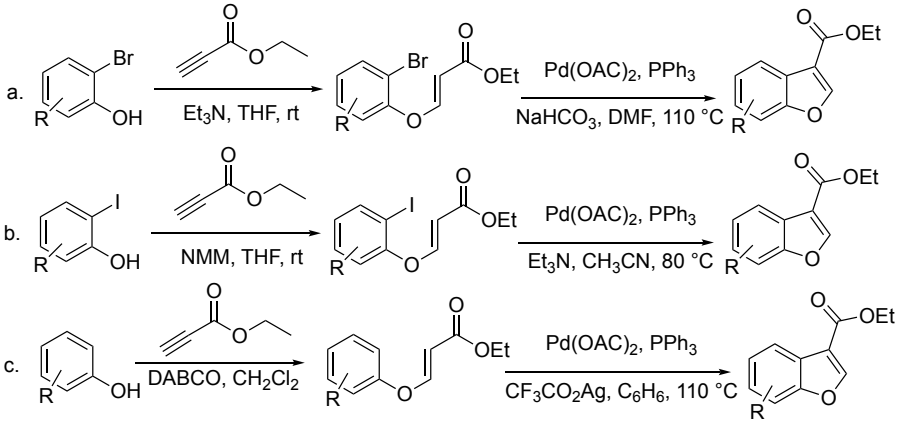
Scheme 1. Synthesis by a thallium catalyzed oxidation annulation

Henke and coworkers reported a new synthetic route to 3-ethoxycarbonyl benzofuran (Scheme 2a).[28] In this two-step procedure, the first step involved the Michael addition of 2-bromophenol with ethyl propionate in the presence of trimethylamine to prepare 3-(2-bromophenoxy)-acrylic acid ethyl ester. Second, a palladium-catalyzed intramolecular Heck coupling of the 3-(2-bromophenoxy)acrylic acid ester created 3-ethoxycarbonyl benzofuran as a yellow oil in 61% yield.

Later, Frontier et al. applied a similar synthetic strategy as reported by Henke et al.[28] involving 3-(2-iodophenoxy)acrylic acid ethyl ester to prepare 3-ethoxycarbonyl benzofuran in 74% yield (Scheme 2b).[29] The ester was produced from the reaction of 2-iodophenol and ethyl propionate in the presence of *N*-methylmorpholine (NMM).

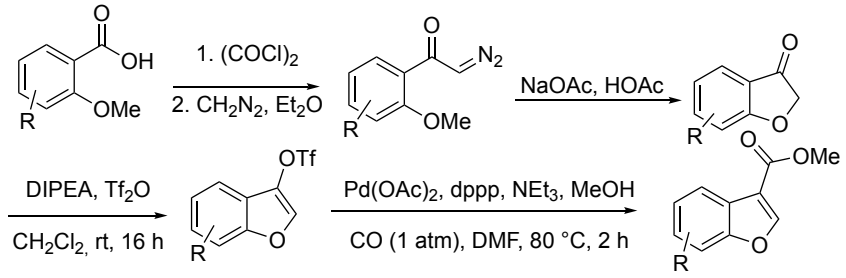
Wang and coworkers reported the formation of 3-ethoxycarbonyl benzofuran in 81% yield from (*E*)-3-phenoxyacrylates through the direct oxidative cyclization by a palladium catalyst (Scheme 2c).[30] The

corresponding acrylates were prepared from phenol and propynoic acid ethyl ester in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO).



Scheme 2. Syntheses by a palladium-catalyzed cyclization

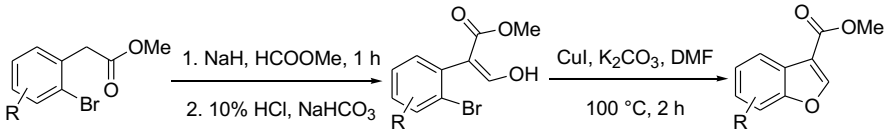
Morice et al. reported the preparation of several 3-methoxycarbonyl benzofurans based on the conversion of 3-coumaranones into their corresponding triflates, followed by palladium assisted CO insertion reactions in methanol (Scheme 3).[31] 3-Coumaranones were prepared from *o*-methoxybenzoic acids with oxalyl chloride and diazomethane followed by decomposition of the diazo ketone in acetic acid/sodium acetate solution.



Scheme 3. Synthesis by a palladium assisted CO insertion

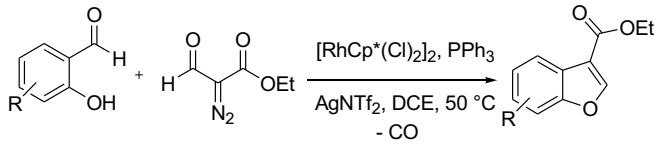
Karchava et al. reported the preparation of 3-methoxycarbonyl benzofuran from hydroxyacrylates. First, the methyl-2-bromophenylacetates

were treated with methyl formate in the presence of sodium hydride and after acidic work up, the mixture provided the acrylate product. Later, a copper-catalyzed cyclization of the acrylate produced 3-methoxycarbonyl benzofuran in 88% yield (Scheme 4).[32]



Scheme 4. Synthesis by a copper-catalyzed cyclization

Recently, in 2016, Yao et al. reported the synthesis of 3-ethoxycarbonyl benzofuran by a Rh(III)-catalyzed reaction between salicylaldehyde and ethyl 2-diazo-3-oxopropanoate in dichloroethane (DCE).[33] Silver triflimide ($AgNTf_2$) favored the formation of 3-ethoxycarbonyl benzofuran via a tandem C-H activation/decarbonylation/annulation process in 72% yield (Scheme 5).

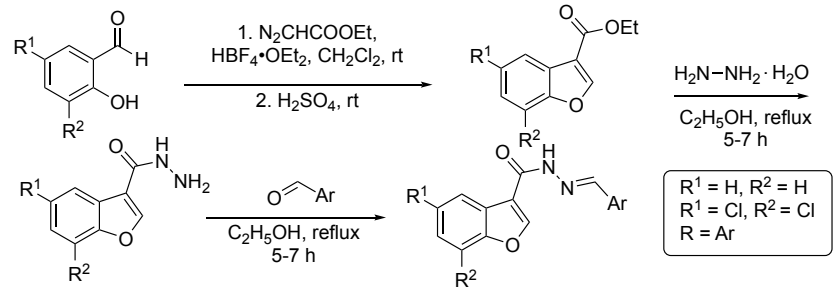


Scheme 5. Synthesis by a rhodium-catalyzed annulation

Applications of our method in organic synthesis

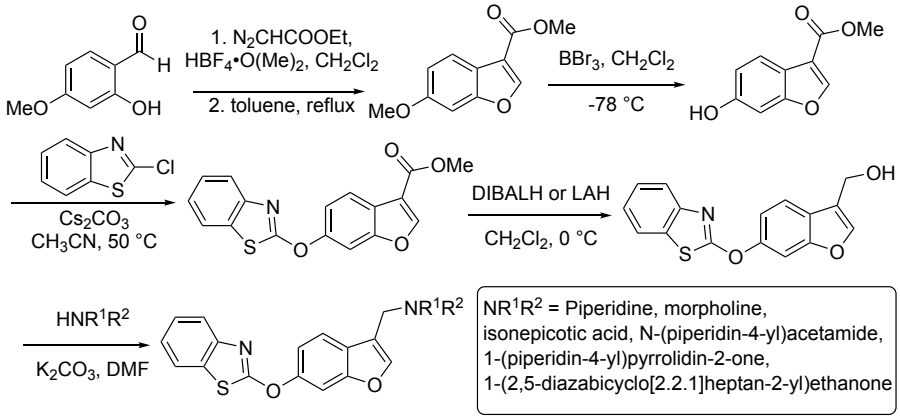
Compared to the alternative syntheses of 3-alkoxycarbonyl benzofuran, our synthetic method is simple, less time consuming, and high yielding with inexpensive and commercially available starting materials. This one-pot synthetic method has been used by us and by other groups in the preparation of several biologically active compounds as described herein.

Telvekar and coworkers synthesized *N'*-benzylidene benzofuran-3-carbohydrazides from 3-ethoxycarbonyl benzofurans (Scheme 6).[34] All these compounds were found to be active against tuberculosis and showed antifungal activity against *Candida albicans*.



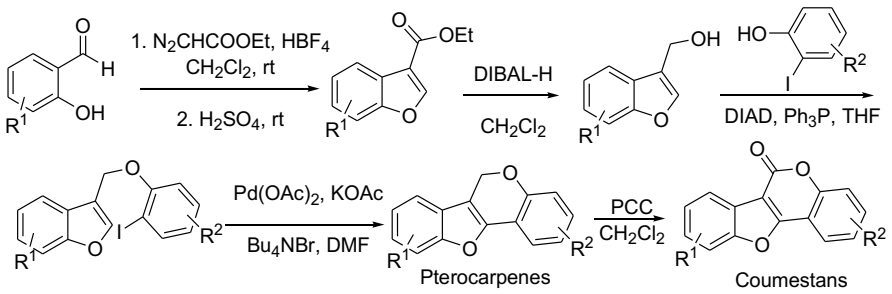
Scheme 6. Synthesis of *N′*-benzylidene benzofuran-3-carbohydrazide

Eccles and coworkers synthesized several leukotriene A_4 hydrolase (LTA_4H) inhibitors from 3-ethoxycarbonyl benzofuran (Scheme 7).[35] LTA_4H inhibitors are used in inflammatory diseases, such as bowel disease, rheumatoid arthritis, chronic obstructive pulmonary disease, and asthma.



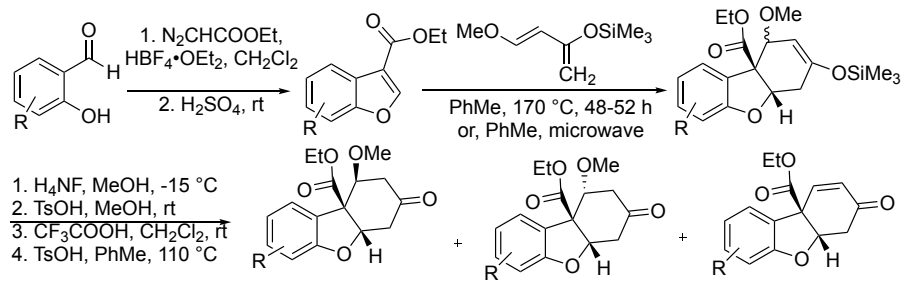
Scheme 7. Synthesis of leukotriene A_4 hydrolase (LTA_4H) inhibitor

Morrow et al. synthesized pterocarpene and coumestan-type heterocycles by the Mitsunobu coupling of 3-(hydroxymethyl)benzofurans with *o*-iodophenols (Scheme 8).[36] Pterocarpans have been shown to exhibit broad spectrum activity against gram-positive bacteria and vancomycin-resistant strains of enterococci. Coumestans, such as coumestrol and flemmichapparin C, have also been shown to display antibacterial, antifungal, and antimyotoxic effects.



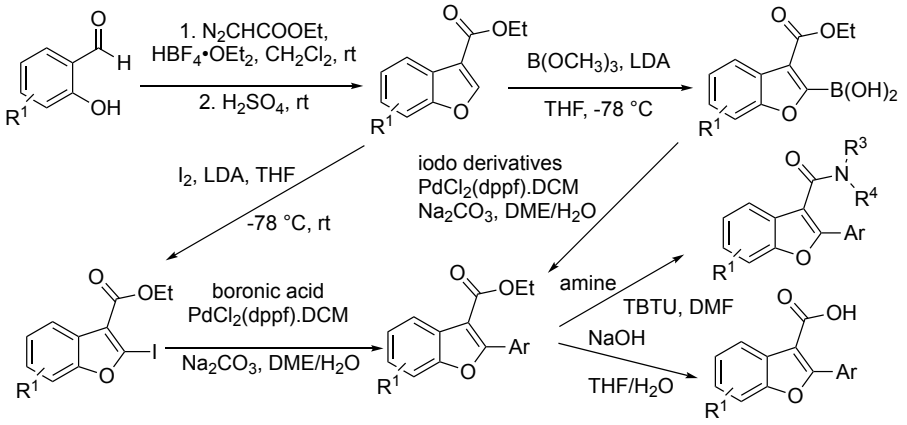
Scheme 8. Synthesis of pterocarpenes and coumestans

Tolstikov et al. reported several regioselective Diels–Alder reactions of Danishefsky's diene with 3-ethoxycarbonyl benzofurans (Scheme 9).[37] These reactions provided effective method for the construction of the heterocyclic skeleton of hexahydrodibenzofuran-7-one and tetrahydrodibenzofuran-7-one. These tricyclic fragments are the structural motifs of many pharmacologically vital substances, such as plant alkaloids morphine, galanthamine, lycoramine, and lunarine, linderol A, and several selective estrogen receptor β -agonists.



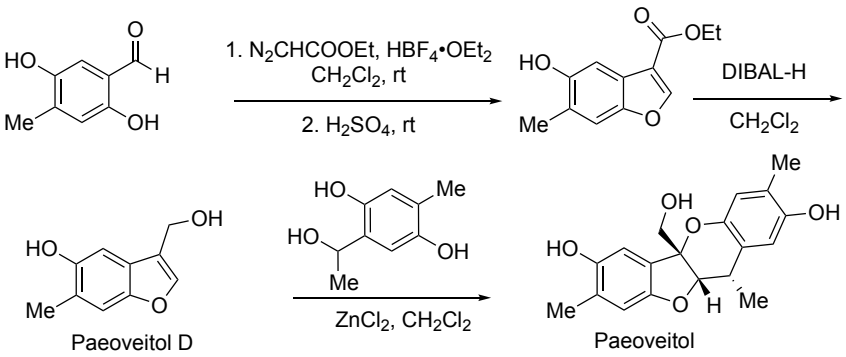
Scheme 9. Construction of heterocyclic skeleton

Elofsson and coworkers constructed a library based on the 3-carboxy 2-aryl benzofuran scaffold from 3-ethoxycarbonyl benzofuran (Scheme 10).[38] These two scaffolds are core components in many biologically active natural and synthetic compounds of which many display a wide range of activities including antiviral, antibacterial, anti-inflammatory, antiangiogenic, and antimitotic activities.



Scheme 10. Synthesis of 2-arylbenzofuran-3-carboxamide derivatives

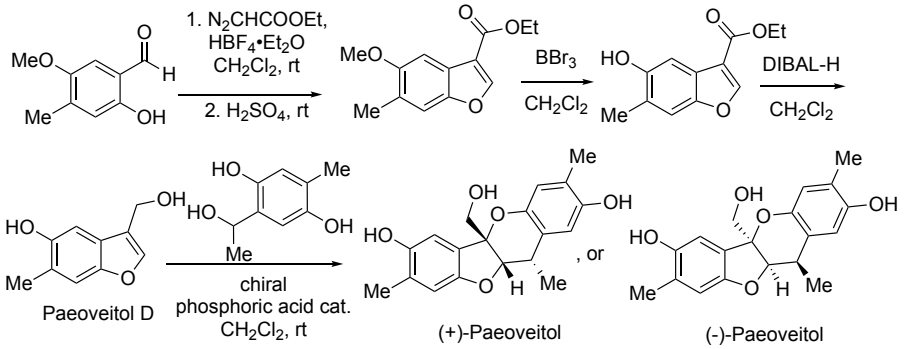
Zhao et al. reported a total synthesis of paeoveitol, the norditerpene natural product which has antidepressant ability, from 3-ethoxycarbonyl benzofuran (Scheme 11).[39] Our published procedure was employed to synthesize 3-ethoxycarbonyl benzofuran, which was reduced to paeoveitol D. Paeoveitol was synthesized by an unusual intermolecular ortho-quinone methide cycloaddition with paeoveitol D with excellent regio- and diastereoselectivity.



Scheme 11. Total synthesis of paeoveitol via paeoveitol D

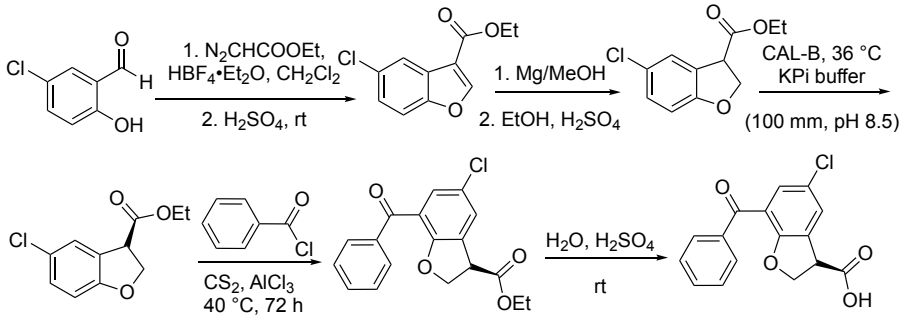
Later, Chen and coworkers reported the first catalytic asymmetric total synthesis of (+)-paeoveitol and (-)-paeoveitol from 3-ethoxycarbonyl

benzofuran via a biomimetic hetero-Diels-Alder reaction in the presence of chiral phosphoric acids as catalysts (Scheme 12).[40]



Scheme 12. Asymmetric synthesis of (+)-paeoveitol and (-)-paeoveitol

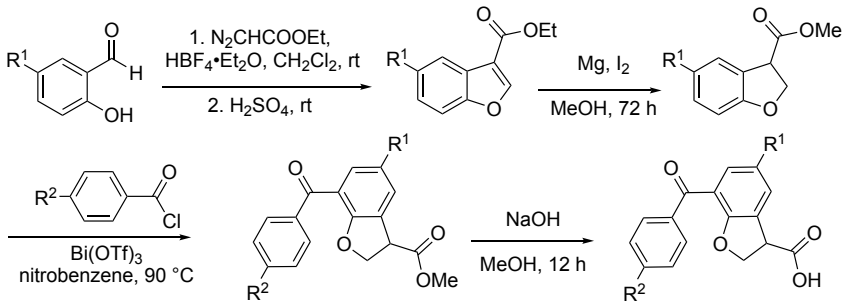
Bongen et al. reported an efficient asymmetric synthesis of 7-benzoyl-2,3-dihydro-1-benzofuran-3-carboxylic acid, BRL-37959 (Scheme 13).[41] 3-Ethoxycarbonyl benzofuran was reduced by magnesium turnings in methanol to form 2,3-dihydrobenzofuran-3-carboxylic acid ethyl ester, which was resolved by dynamic kinetic resolution. Friedel-Crafts acylation reaction of the enantiopure product followed by acidic hydrolysis produced (*R*)-BRL-37959, which acts as analgesic agents with low gas irritancy.[5]



Scheme 13. Synthesis of enantiopure (*R*)-BRL-37959

Recently, in 2018, our group reported the synthesis of 7-benzoyl-2,3-dihydro-1-benzofuran-3-carboxylic acid, BRL-37959 and its analogs from 3-ethoxycarbonyl benzofuran (Scheme 14).[42] To synthesize BRL-37959,

incorporation of a benzoyl group at the C-6 position of benzofuran ring by the Friedel-Crafts acylation reaction was the main challenge. Our recent method demonstrates that bismuth (III) trifluoromethanesulfonate can be used as a catalyst for the Friedel-Crafts acylation reaction with good yield. This efficient method allowed the production of many analogs of BRL-37959 in high yield.



Scheme 14. Synthesis of BRL-37959 and its analogs

In summary, 3-ethoxycarbonyl benzofuran plays a pivotal role in the field of medicinal and pharmaceutical chemistry. The concise synthesis of 3-ethoxycarbonyl benzofuran was reported by our group with excellent yield from commercially available starting materials. In this addendum, we discussed several alternate methods for the preparation of 3-ethoxycarbonyl benzofuran and applications of our published method to synthesize important biologically active compounds. In the future, our developed method of preparing 3-ethoxycarbonyl benzofuran could be a valuable procedure in making benzofuran-ring containing natural and unnatural products.

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Mizzanoor Rahaman received his BS and MS degree in Chemistry from the University of Dhaka, Bangladesh. He began PhD studies in Organic Chemistry at the University of Wisconsin-Milwaukee in 2013. Since then he has been an active member in Professor Hossain group and has received multiple Chancellor's Fellowship Awards. He was awarded an ACS Milwaukee Section Travel Grant in 2018. He was also honored with the University's Outstanding Teaching Assistant Award for 2017.